IN THE UNITED STATES DISTRICT COURT
IN AND FOR THE SOUTHERN DISTRICT OF NEW YORK

ASSOCIATION FOR MOLECULAR PATHOLOGY, et al., Plaintiffs, v. UNITED STATES PATENT AND TRADEMARK OFFICE, et al., Defendants.	CASE NO. 09-CV-4515 (RWS)

BRIEF FOR *AMICI CURIAE*

(BayBio, Celera Corporation, The Coalition for 21st Century Medicine, Genomic Health, Inc., QIAGEN, N.V., Target Discovery, Inc., and XDx, Inc.)

IN SUPPORT OF DEFENDANTS' OPPOSITION TO PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

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I. INTRODUCTION

Plaintiffs are asking this Court to reinterpret constitutional and statutory principles to undermine Myriad's patent portfolio in a way that could have far-reaching implications on a diagnostic personalized medicine industry that is committed to improving patient care. Plaintiffs have painted a dark picture of Myriad and the implications for patients if Myriad is allowed to maintain its current patent exclusivity over the use of BRCA1/2 genes.[1] *Amici Curiae* are sensitive to the fears expressed by Plaintiffs in this case, and believe that the Court has a panoply of appropriate patent remedies at its disposal to provide redress, if appropriate and necessary. However, in attacking the legality of DNA sequence patents and associated diagnostic method patents, and Defendants' legal assertion of such patent rights, Plaintiffs ask this Court to take aim at a patent foundation underlying the entire genetic testing and biological drug industries.

Personalized medicine relies, in part, on genetic testing, and it holds great promise for all of us, as *Amici* explain below. The diagnostics that are developed for use in personalized medicine involve thousands upon thousands of man hours of intensive research that costs hundreds of millions of dollars. The foundations of our current patent system support this industry. There is no question that our current, carefully-crafted patent system with its well developed body of case law has served this country well, fueling advances in medical research that have promoted what may be the largest societal prize for all of us: greater longevity with higher quality of health.

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[1] In contrast to Plaintiffs' assertions, Myriad invests enormously in "research, development, insurance coverage, and more importantly in raising patient and physician awareness and understanding of the [BRCA] tests." (Declaration of Dr. Gregory C. Critchfield (Critchfield Decl.), ¶ 25.)
"To date, Myriad has performed over 400,000 BRACAnalysis® tests … from all 50 states. Over 40,000 healthcare providers have ordered and used the test … [m]ore than 90% …are covered by insurance, and the average reimbursement rate is over 90% of the cost of the test." (Critchfield Decl. ¶ 25.) "The weighted average out-of-pocket cost to each patient is less than $100." (Critchfield Decl.¶ 32.)
"There are more than 2,600 insurance payors who reimburse for the BRACAnalysis ® test. There are more than 80,000 insurance plans that cover the BRACAnalysis ® test." (Critchfield Decl, ¶ 25.)

As explained below, academic and government research cautions against undermining the current patent system, which Plaintiffs' overreaching theories effectively seek to do. That system itself, while appropriately expansive in the definition of patentable subject matter, contains numerous checks and balances on the grant of patents themselves, and further gives this Court broad latitude to fashion remedies that serve the patentees and the public interest. The relief requested would effectively outlaw all DNA sequence patents, and potentially all methods of their use. The suggested use of such a blunt and destructive instrument is neither necessary nor desirable in view of available alternative judicial tools and the competing interests, as we explain below.

At the end of the day, a fundamental question before this Court, whether DNA sequence patents constitute patentable subject matter, is a societal question that should be left to Congress. Numerous bills have been introduced in Congress over the years to address and fine-tune the patent issues that surround DNA sequence and methods of use patents. Tellingly, none of these legislative efforts have called into question whether such DNA sequence patents are within Congress' statutory definition of patentable subject matter set forth in 35 U.S.C. § 101.

Amici respectfully request that the Court deny Plaintiffs' motion for summary judgment.

II. STATEMENT OF INTEREST OF *AMICI CURIAE* AND EXPLANATION OF THEIR DIAGNOSTIC PRODUCTS[2]

A. GENOMIC HEALTH, INC.'S STATEMENT OF INTEREST AND EXPLANATION OF ITS ONCO*TYPE* DX® BREAST CANCER ASSAY

Genomic Health Inc. is a life science company that is committed to improving the quality of cancer treatment decisions through genomics-based clinical laboratory services. The company currently offers the Onco*type* DX breast cancer assay, which predicts the likelihood that a patient with early-stage, ER-positive breast cancer will experience a recurrence within 10 years and whether that patient will benefit from adding chemotherapy to his/her hormonal therapy. The test is based on mRNA levels of 21 genes, and provides an individualized

[2] The *Amici* state that this brief was not authored in whole or in part by counsel to a party, and that no monetary contribution to the preparation or submission of this brief was made by any person or entity other than these *Amici Curiae* or their counsel.

Recurrence Score® (RS) result for each patient that is a personalized risk estimate. For example, a patient with a lower score (RS < 18) will not significantly benefit from the addition of chemotherapy, and may be treated with hormonal therapy alone. Considering that about 50% of early-stage, ER-positive breast cancer patients without lymph node involvement are in this category, this could represent substantial savings to the health care system and a benefit to those patients who are spared the unnecessary disruption and toxic effects of chemotherapy. On the other hand, a higher score (RS > 30) signals that chemotherapy should be added to the patient's regimen. Used in concert with other clinical factors, the Onco*type* DX assay can aid physicians and patients in making personalized and cost-efficient treatment decisions. The Onco*type* DX breast cancer assay is recommended in both the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) clinical practice guidelines, and has been used by 130,000 breast cancer patients from over 50 countries.

The selection and validation of Onco*type* DX genes, identified from potentially thousands of genes, was the culmination of thousands of hours of research by highly trained scientists at Genomic Health. This effort could not have been conducted without outside investment, and the company's patent portfolio is an important tool for attracting and maintaining investors. In exchange for making all of its cancer biomarkers, assay platform technology, and validation study data public, Genomic Health has received multiple patents covering the methods and systems used to provide this valuable genomic information.

Genomic Health is committed to making the Onco*type* DX assay available to patients and encouraging independent research in the area of oncology. The Genomic Access Program (GAP) provides financial assistance and payment plans to eligible patients with financial hardship and uninsured/underinsured patients, supports insured patients through the claim submission process, conducts benefit investigations, and advocates on behalf of patients if claims are denied. Additionally, Genomic Health supports continued research and clinical studies in many areas of oncology. In 2008, Genomic Health provided approximately $1.4 million in grants for collaborative research, and provided over $1 million in free services to advance

scientific research in molecular biology, oncology, and cancer treatment, and to allow independent researchers to confirm the accuracy of Onco*type* DX in various breast cancer patient populations. For example, the National Cancer Institute (NCI) and the Eastern Cooperative Oncology Group (ECOG) are using Onco*type* DX to identify and assign treatment to more than 10,000 breast cancer patients from 900 sites worldwide. This trial will evaluate the effect of adjuvant chemotherapy for patients with an intermediate RS to evaluate and improve treatment decision-making for this sub-category of patients. Genomic Health is making this trial possible by assuming financial responsibility for all tests, or patient co-payments, that are not covered by insurance. Like many diagnostic companies, Genomic Health uses its success to benefit patients and re-invest profits back into scientific research.

B. CELERA CORPORATION'S STATEMENT OF INTEREST AND EXPLANATION OF ITS PERSONALIZED MEDICINE DIAGNOSTICS

Celera Corporation is a manufacturer of diagnostic products that include gene-based products used in genetic testing. Celera's wholly-owned subsidiary, Berkeley HeartLab, Inc., is a CLIA-certified laboratory that provides clinical laboratory testing services, including genetic testing services. Celera relies on intellectual property protection in advancing its business, particularly patents relating to various genes, genetic mutations, and methods of their use in diagnostic testing.

Among Celera's product offerings, its diagnostic test kit for cystic fibrosis best exemplifies the successful commercialization of a medically-important product made possible through licensing of DNA sequence-based patents. Cystic fibrosis is an inherited genetic disorder that often results in death during early adult years due to lung infections. It is caused by a number of genetic mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The American College of Obstetricians and Gynecologists currently recommends that couples planning a pregnancy or seeking prenatal care be screened for cystic fibrosis gene mutations to help them make informed reproductive decisions.

The CFTR gene and a number of its disease-associated genetic mutations have been patented by the universities where the original discoveries were made. These different

universities have made their DNA sequence-based patents available to commercial entities through licensing arrangements in order for diagnostic products to be developed and brought to patients. Celera has entered into agreements with the patent owners for non-exclusive licenses to the relevant patents, has obtained FDA clearance to commercialize a diagnostic product utilizing the patented DNA sequence-based technologies, and has become the leading provider worldwide of such cystic fibrosis testing products. Thus, these licensing arrangements have provided Celera and other companies access to critical DNA sequence-based patents for commercial development, and Celera's product has made cystic fibrosis testing widely available.

The university patent owners, who are not equipped to exploit their patents through commercial activities, have generated royalty revenue from Celera's product sales. Most importantly, it is the general public that has benefited because of the availability of this genetic testing. Based on Celera's experience, DNA sequence-based patents and related licensing practices have served the academic research institutions, the diagnostic testing industry, and patients well.

Celera has also sought patent protection for its own genetic discoveries. Over the past eight years, Celera has invested over $200 million in its discovery research efforts, primarily focused on the discovery of association of genetic mutations with risk for complex diseases. These inventions are covered in a number of Celera's patent filings.

Based on these proprietary discoveries, Celera's wholly-owned subsidiary, Berkeley HeartLab, Inc., has commercialized laboratory-developed tests that predict increased risk for heart disease and treatment response by detecting two novel genetic mutations. The first mutation is in a gene known as KIF6, which has been shown to confer to carriers up to a 55% increased risk of developing a cardiovascular event, such as a heart attack. In carriers of the KIF6 genetic mutation, studies of samples from landmark clinical trials have demonstrated that patients' incremental cardiovascular risk can be substantially and significantly reduced by statin therapy. Celera has out-licensed its KIF6 invention to third party laboratories to enable them to develop and commercialize their own genetic testing services.

The second mutation is in a gene known as LPA, which has been shown to confer to carriers up to a 100% increased risk of having a cardiovascular event, such as a heart attack. In carriers of the LPA genetic mutation, studies have demonstrated that patients' incremental cardiovascular risk can be substantially and significantly reduced by low-dose aspirin therapy, whereas aspirin-treated non-carriers have a substantially increased risk of life-threatening bleeding events for every cardiovascular event avoided.

These novel genetic tests are used in personalized medicine today by providing medically-relevant genetic information to patients, i.e. carriers of either of these genetic mutations are not only informed of their increased risk for a heart attack, but are also informed that they are more likely to benefit from a particular form of treatment, thereby increasing their likelihood of medication compliance and reducing the development of a cardiovascular event. These significant genetic discoveries would not have been made without a substantial investment over a long period of time.

In Celera's experience, meaningful gene-disease associations are confirmed only if the initial discoveries are followed by large scale replication and validation studies using multiple sample sets, which cannot be performed without considerable commitment of capital and resources. In order to attract outside investment to fund the costly pursuit of genetics research and the subsequent development of a commercial product, companies like Celera must rely on patent protection for their discoveries. The prospect of a patent and, thus ownership, are a critical consideration for investors who provide funding for such research and invariably look to patents that result from such work as a way of protecting and harvesting their investment.

C. QIAGEN, N.V.'S STATEMENT OF INTEREST AND EXPLANATION OF ITS MOLECULAR DIAGNOSTIC PRODUCTS

QIAGEN was founded in 1984 by scientists from the Heinrich-Heine University in Dusseldorf, Germany, and today has operations around the world, employing more than 3,500 people. QIAGEN is a leading provider of innovative sample and assay technologies and products which are considered standard for use in molecular diagnostics, applied testing, and academic and pharmaceutical research and development. QIAGEN's products standardize

workflows and enable customers to reliably and rapidly process samples from collection through purification and analysis of the target molecules.

QIAGEN offers more than 500 consumable products and automated solutions, and sells these products to clinical diagnostics laboratories; customers in applied testing markets, such as forensics, animal or food testing, and pharmaceutical process control; academic research centers; and pharmaceutical and biotechnology companies. These products enable the customers to efficiently pursue their research and commercial goals that require the analysis of nucleic acids. In the fast-growing market for molecular diagnostics, QIAGEN's menu of more than 120 molecular diagnostic tests is among the broadest in the entire industry, including numerous certified tests (over 40 are CE-marked) that fulfil regulatory requirements and can be run on automated platforms. These tests include the first FDA approved assay for HPV (human papillomavirus) screening (the digene HPV test®).

QIAGEN invests heavily in innovation. Nearly 600 employees in research and development, who work in seven centers of excellence on three different continents, constantly develop new applications that meet the needs of its customers. QIAGEN's product development efforts are focused on expanding the features and applications of existing products and developing innovative new products in selected areas where QIAGEN has expertise and has identified substantial unmet market needs. QIAGEN's annual total research and development expenditure exceeds $120 million.

QIAGEN believes that molecular diagnostics have fundamental advantages over traditional diagnostic technologies, such as immunoassays, in potential applications and clinical utility as defined by specificity and sensitivity. Molecular diagnostics can be used, for example, to detect or identify pathogens such as microorganisms, cancer cells, bacteria and viruses by searching for their specific nucleic acid sequences. In order to prove that a pathogen which causes a disease is present in a patient, the unique sequence of the target DNA or RNA nucleic acid causing the disease must be known, and either the target sequence in the sample must be amplified (target amplification) or the signal from the DNA must be amplified (signal

amplification) to allow detection. Such techniques have been enabled by recent advances in molecular analysis technologies.

In addition, clinical sensitivity and specificity can be greatly enhanced for certain diagnostic assays using nucleic acid-based information. Clinical sensitivity is typically regarded as the measure of a test's ability to accurately detect the presence of disease. A false negative test result can lead to providing a negative or normal diagnosis to a patient who carries the infection. Clinical specificity is typically regarded as the measure of a test's ability to correctly identify the absence of disease when it is not present. A false positive test result can lead to providing a positive or abnormal diagnosis to a patient who does not carry the infection.

An example of how molecular diagnostics can reduce mortality is QIAGEN's development of HPV diagnostics. HPV is a common virus that infects the skin and mucous membranes. There are about 100 types of HPV. Approximately 30 of those are spread through genital contact (typically sexual intercourse). Around 12 – called "low-risk" types of HPV – can cause genital warts. In addition, there are approximately 15 "high-risk" types of HPV that can cause cervical cancer. Worldwide, cervical cancer is the second-most-common type of cancer that strikes women – behind only breast cancer. In the United States, cervical cancer is the 14th most common cause of new cancers diagnosed among women every year. The American Cancer Society estimates that in 2007, about 11,150 women in the United States developed cervical cancer and about 3,700 died from it. In each and every case, an infection by HPV has been linked to this cancer. The discovery of this connection has been awarded by a Nobel prize award in 2008.

For detection of HPV, QIAGEN sells in the United States primarily for the two FDA-approved indications: adjunctive primary screening with a Pap test for women age 30 and older, and follow-up testing of inconclusive Pap test results in women of any age. Molecular diagnostics (like QIAGEN's products) have been shown to provide higher specificity together with clinical sensitivity for HPV infections compared to the old-fashioned Pap test. By developing the first FDA approved molecular diagnostic test for HPV, QIAGEN has

revolutionized HPV detection. The time, money and resources required for new product approvals by the FDA and foreign regulatory authorities are very significant upfront investments that could not be made without protection for the technology and results generated.

While proper intellectual property protection allows for said upfront investments, it also provides for social investments. QIAGEN*cares* is the cornerstone of a comprehensive Corporate Social Responsibility Program established by QIAGEN. With this platform, QIAGEN has created an umbrella for the support of initiatives that help to improve lives by aiding in the fight against diseases in which the company's products can play an important role, be it research, surveillance or diagnosis of diseases.

Cervical cancer is a major problem in emerging regions. Most of the cases are registered there. In 2009, QIAGEN entered into a partnership with the Chittaranjan National Cancer Institute to establish the first large-scale cervical cancer screening program in Kolkata, India. The initiative, which is part of the QIAGEN*cares* program, will benefit 50,000 women over the next five years.

On April 1, 2009, QIAGEN announced the donation of one million of its HPV tests to bring cervical cancer screening to the world's developing nations. The HPV tests will be donated over a five-year period to benefit the countries most in need as determined by gross national income and annual income per capita. QIAGEN works closely with global health advocates and public health partners to select and serve appropriate recipient groups in the most effective manner.

In close cooperation with the Bill & Melinda Gates Foundation, QIAGEN promotes broader access to life-saving diagnostics including careHPV and donations for tests to cervical cancer screening projects in China. careHPV is an HPV testing technology that has been specifically designed for low-resource settings.

QIAGEN and its customers operate in a highly regulated environment characterized by continuous changes in the governing regulatory framework. Genetic research activities as well as products commonly referred to as "genetically engineered," such as certain food and

therapeutic products, are subject to governmental regulation in most developed countries, especially in the major markets for pharmaceutical and diagnostic products (i.e., the European Union, the United States, and Japan). QIAGEN's position is comparable to the position of innovative drug companies. The ability to improve people's lives strongly depends on the possibility to recover the high upfront investments in the commercialization of diagnostic tests, including investments in extensive and expensive clinical trials to gain approval by the FDA. A major factor is the ability to protect discovered technology by patents. Without patent protection the investment of hundreds of millions of dollars required to discover a disease marker, validate it, transform it into a diagnostic assay, have it approved by the FDA, and finally bring it to the patient, would not be possible and innovative products would no longer be commercially sustainable. If QIAGEN's upfront investments in marker discovery and validation could be used by third parties without proper compensation to QIAGEN, QIAGEN's high R&D budget would decrease significantly and its capability of funding clinical trials would be at severe risk.

D. XDx, Inc.'s Statement of Interest and Explanation of Its AlloMap® Molecular Expression Testing

XDx is a molecular diagnostics company focused on the discovery, development and commercialization of non-invasive gene expression testing in the areas of transplant medicine and autoimmunity. The company uses modern genomics and bioinformatics technology to develop molecular diagnostic assays based on gene expression patterns in blood cells that provide clinically useful information. Gene expression patterns reflect the activity of genes in the various blood cells types at the time the sample was taken. Overall gene activity in a blood sample can be affected by drugs, immune activation, inflammation, or by recruitment of new cells from the bone marrow. Developing these novel in vitro diagnostic tools requires analysis of carefully characterized blood samples to find marker genes that are differentially expressed, either at a higher or lower level, in different disease states.

Gene expression is initially evaluated using microarrays, which take advantage of the recently defined sequence of the entire human genome to assess the expression of most genes in the genome on a single glass slide. Using sophisticated bioinformatic tools, candidate marker

genes are identified from among the more than 41 thousand features assessed in the microarray data. The most promising candidates are then tested using quantitative real-time PCR (qRT-PCR), which is a more sensitive and reproducible technique for measuring gene expression levels than microarrays, to find markers where differential expression is confirmed in the two clinical states. From this list of confirmed marker genes, computer algorithms are used to identify the combination that best discriminates one clinical state from the other. The final product of the development process is a list of genes to be assessed, their corresponding qRT-PCR assays, and a mathematical algorithm that combines the resulting expression levels into a score that provides information regarding the clinical state that existed when the blood sample was collected. This product has then been validated using an entirely new set of samples form other patients to establish the performance characteristics of the test.

Using this approach, XDx has developed AlloMap® Molecular Expression Testing for heart transplant patient management based on a proprietary method of utilizing gene expression in blood. The molecular expression technology may be applicable to post-transplant management for other organs, and is currently being explored to assist with other diseases that involve the immune system, such as autoimmune and chronic inflammatory diseases.

XDx is committed to supporting patients through the transplantation process. For example, the company sponsors "TransplantBuddies," a community support site, as well as a patient advocacy program that helps patients to resolve AlloMap billing-related issues. In addition, XDx offers financial aid to qualified patients.

E. TARGET DISCOVERY, INC.'S STATEMENT OF INTEREST AND EXPLANATION OF ITS ISONOSTIC™ DIAGNOSTIC BIOMARKERS

Target Discovery discovers, validates, and utilizes protein isoforms to improve clinical diagnosis and management of disease. A growing body of scientific literature shows that protein isoforms correlate more precisely with disease state and patient-specific treatment response than current clinical biomarkers. Most protein isoforms (90%) are made by the body after the protein is produced (post-translational modifications). Such protein modifications remain largely inaccessible to current immunodiagnostic and nucleic acid clinical assays. Target

Discovery's Isonostic™ products are designed to make this isoform biomarker information accessible to clinicians.

Isoforms represent a new class of diagnostic biomarkers. Our bodies have developed elaborate mechanisms to modify proteins, creating many protein variants (isoforms), both to increase the diversity of functions and to regulate the activities of proteins. About 8% percent of these isoforms are generated during the process of transcribing the coding genes into mRNA. Over 90% of protein isoforms are created through post-translational modifications (PTMs) after the mRNA is translated into a protein. Recent scientific evidence is demonstrating that the differentiation and quantification of individual protein isoforms could improve insights into disease diagnosis and management. Target Discovery's Isonostic assays are designed to access and capitalize upon these untapped protein isoform biomarkers. The rapidly growing field of nucleic acid molecular diagnostics is only able to address 8% of the potential isoform biomarker space: those isoforms generated at the mRNA level. Furthermore, the correlation between mRNA and protein levels is poor. Except in rare cases (e.g., the HgA1c diabetic assay) immunodiagnostic assays fail to distinguish between the isoforms of a particular parent protein, explaining the stagnant growth of this diagnostics market segment and the loss of market share to molecular diagnostics.

Target Discovery has selected oncology as its initial focus for Isonostics development, in critical applications where existing diagnostics are unavailable or inadequate. Isoforms have been shown to be clinically relevant across wide-ranging application in cancer care, such as diagnosis, staging, treatment, systemic effects, and drug toxicity. Clinical research is revealing that isoform changes are critically relevant, and there are compelling motives for improved patient outcomes and for significant health economic benefits. The company’s initial Isonostic products are targeting critical chemotherapy treatment guidance decisions in ovarian cancer and lung cancer.

Outside of our cancer focus, Target Discovery works with companies to develop Isonostic assays for other diseases where protein isoforms are known or suspected to be useful

biomarkers. The development of assays to determine patient-specific response profiles relative to drug efficacy or toxicology (Theranostics) is an area that holds great promise for personalized medicine.

F. BAYBIO'S STATEMENT OF INTEREST

BayBio is an independent, non-profit 501(c)(6) trade association serving the life science industry in Northern California. BayBio represents more than 330 companies involved in the research and development of treatments, cures and diagnostics. Of its life sciences members, more than 30 organizations develop diagnostic services intended to improve health care outcomes. Many of these organizations employ fewer than 100 people and spend between $25 million to $60 million annually on research and development.

G. THE COALITION FOR 21ST CENTURY MEDICINE'S STATEMENT OF INTEREST

The Coalition for 21st Century Medicine represents some of the world's most innovative diagnostic technology companies, clinical laboratories, researchers, physicians, venture capitalists, and patient advocacy groups -- all linked by a common mission to develop advanced diagnostics that improve the quality of healthcare for patients. The Coalition believes that continuous diagnostic innovations are necessary to assure that timely and accurate information is available when decisions regarding diagnosis, prognosis, and therapy need to be made. This future is threatened by growing efforts to undermine "gene patents" (*i.e.*, DNA sequence patents) in the United States. Though these movements promise to increase patient access to their molecular and genetic information by removing patent protection for the underlying inventions, the ultimate impact will be exactly the opposite. This is because, without the exclusivity provided to inventors in all other industries, investors will move away from diagnostic and biologic technology. Without their continued investment, the Coalition believes that private industry will no longer be able to support the expensive and complex research, development, and commercialization of these healthcare products in the future. In effect, research in advanced diagnostics will violently contract, and this will cause serious harm to the quality of healthcare for patients in the near future. Universities and research institutes cannot

pick up this slack because they lack the know-how, resources and regulatory expertise necessary to bring such innovations to market.

III. PATENT EXCLUSIVITY IS REQUIRED FOR INVESTMENT TO COMMERCIALIZE PERSONALIZED MEDICINE

Rather than seeking relief for the specific alleged actions by defendant Myriad, Plaintiffs are asking this Court to rule on the constitutionality of DNA sequence patents (erroneously identified by Plaintiffs as a patent on the gene itself as it exists in nature) and associated method claims, as well as the authority of the U.S. Patent and Trademark Office (USPTO) to exercise its discretion in this area. This Court should be keenly aware that such a finding could negatively impact the diagnostic industry, as well as the therapeutic industry that also relies, in part, upon DNA sequence patents to protect its products. Without patent exclusivity, diagnostic companies would struggle to attract the investment necessary to drive future research, and innovation in this area would contract. Thus, Plaintiffs' requested relief not only threatens to drive diagnostic companies out of business, which would negatively impact the U.S. economy, but would actually reduce patient access to the power of molecular information and information about who would benefit from future therapies.

A. THE PROMISE OF PERSONALIZED MEDICINE

Personalized medicine refers to the tailoring of medical treatment to the individualized characteristics of each patient. Such individual characteristics are determined by diagnostic testing, often genetic testing of an individual's DNA sample. Personalized medicine allows physicians and patients to make treatment decisions based on biological markers, including gene-based DNA sequences and their variations, that signal the presence or risk of developing a disease, the likelihood that the patient will respond to particular therapies, and the expected patient outcome. Diagnostic correlations used to identify the most effective treatment options for an individual patient are critical to personalized medicine. The use of diagnostic correlations to select the optimal therapy for an individual patient translates to improved and more cost-efficient health care for all. There are two important issues in selecting a treatment: efficacy and risk of side effects. For example, in treating selected diseases, commercial drugs

work only in 30-60 % of the target population.[3] Further, most drugs and biological therapeutics have undesirable side effects, some of which can be predicted based on a patient's drug metabolism genetic signature. Published estimates show that approximately 5.3% of hospital admissions are associated with adverse drug reactions (ADRs).[4]

Access to a patient's genetic information may help physicians to determine whether a patient will respond to a particular therapy, and whether the risk of disease for that patient justifies the expense and burden of particular therapy. This information has the potential to increase patient adherence to treatment regimens and decrease costs and failure rates of drug clinical trials by focusing on appropriate sub-classifications of patients. It is no wonder, then, that the FDA has recognized and encouraged the development of personalized medicine pharmacogenetic information, and nearly every major pharmaceutical project is incorporating information on genetic variation and its effects on the safety and effectiveness of the candidate drug.[5]

The importance of supporting the further development of personalized medicine has also been recognized by the President's Council of Advisors on Science and Technology (*2008 Report on Priorities for Personalized Medicine*)[6], the U.S. Dept. of Health & Human Services (*Personalized Health Care Initiative*), the Legislature (*Genomics and Personalized Medicine Act of 2006*, S. 3822, 109th Cong. (2006) Obama),[7] and rules and comments put forth by many other professional, state and federal health care organizations. In her written testimony during Senate confirmation hearings, HHS Secretary Kathleen Sebelius made the following statement:

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[3] *See, e.g.*, B. Spear, et al., *Clinical Application of Pharmacogenetics,* 7 TRENDS MOL. MED. 201 (2001) (Declaration of William G. Gaede, III (Gaede Decl.), Ex. 1, filed in support hereof).
[4] C. Kongkaew, et al., *Hospital Admissions Associated with Adverse Drug Reactions: A Systematic Review of Prospective Observational Studies*, 42 THE ANNALS OF PHARMACOTHERAPY 1017 (2008) (Gaede Decl., Ex. 2.).
[5] *See, e.g.*, U.S. Dept. of Health and Human Servs. and U.S. Food and Drug Admin., Guidance for Industry on Pharmacogenomic Data Submissions (March 2005) (Gaede Decl., Ex. 3); U.S. Dept. of Health and Human Servs. and U.S. Food and Drug Admin., Drug-Diagnostic Co-Development Concept Paper (2005) (Gaede Decl., Ex.4); 21 C.F.R. § 201.57.
[6] Gaede Decl., Ex. 5.
[7] Gaede Decl., Ex. 6.

> As a result of these contributions to improvement in the quality of care, personalized medicine represents a key strategy on healthcare reform. The potential application of this new knowledge, especially when supported through the use of health information technology in the patient care setting, presents the opportunity for transformational change.[8]

In sum, personalized medicine offers a model for efficient and high quality health care. Diagnostic companies that offer these tools are dedicated to working with federal agencies, physicians, patients, and payers to make the much-awaited transformation of healthcare possible.

B. R&D TO IDENTIFY GENES, THEIR USEFUL SEQUENCES, GENETIC VARIATIONS, AND THEIR DISEASE CORRELATION IS COSTLY

The biotechnology industry in the United States has grown enormously over the years. In the United States, there are over 1,452 biotechnology companies that provide medical therapies and diagnostics, agriculture, and industrial processes. Approximately 20% of these are publicly traded, generating revenues in excess of $60 billion and employing approximately 9 million people. Biotech is one of the most research-intensive industries in the world, with U.S. public companies spending more that $27 billion to develop new products. In the health care sector, the biotechnology industry has more than 370 therapeutic products currently in clinical trials being studied to treat more than 200 diseases.

Given the long and expensive research, development, and commercialization cycles, and relatively limited resources of most personalized medicine companies, the patent system is essential to protect and foster innovation that, in turn, attracts financial investors. Although Plaintiffs allege injuries only with respect to the unique patent portfolio and business model of defendant Myriad, the remedies sought by Plaintiffs could potentially cause investors to question the stability of an industry that, like many others, is founded on the limited exclusivity of patented technology. It is particularly troublesome that Plaintiffs are seeking such an outcome without a full trial on the unique facts and implications underpinning their novel legal theories. In short, Plaintiffs are seeking to punish defendant Myriad for asserting its unique patent portfolio to allegedly "preclude all research into genes known to correlate with an increased risk

[8] Opening Statement of Kathleen Sebelius, Senate Committee on Finance (April 2, 2009) (Gaede Decl., Ex. 7).

of breast and/or ovarian cancer."[9] However, by attacking the very foundation of DNA sequence patents, Plaintiffs have raised what should be a simple patent dispute into a high-stakes fight that could result in the loss of future diagnostic R&D and a bleak outlook for patients and the health care system.

C. ACADEMIC AND GOVERNMENT RESEARCH ESTABLISHES THAT A STRONG PATENT SYSTEM IS A NECESSARY CONDITION TO FOSTER RESEARCH AND DEVELOPMENT THAT BENEFITS PATIENTS

Considerable academic and government research supports the benefits of a strong patent system to fostering innovative research and development that, in turn, fosters human longevity. Indeed, amicus American Medical Association has endorsed the concept of DNA sequence patents as advancing the development of therapies. American Medical Association Ethics Opinion 2.105 (2007)[10] states, in part:

> A patent grants the holder the right, for a limited amount of time, to prevent others from commercializing his or her inventions. At the same time, the patent system is designed to foster information sharing. Full disclosure of the invention--enabling another trained in the art to replicate it--is necessary to obtain a patent. Patenting is also thought to encourage private investment into research. Arguments have been made that the patenting of human genomic material sets a troubling precedent for the ownership or commodification of human life. ***DNA sequences, however, are not tantamount to human life***, and it is unclear where and whether qualities uniquely human are found in genetic material. ***Genetic research holds great potential for achieving new medical therapies***. It remains unclear what role patenting will play in ensuring such development. ***At this time the Council concludes that granting patent protection should not hinder the goal of developing new beneficial technology and offers the following guidelines*** . . . .

Academic research has established a connection between strong research and development and the cost savings and benefit to human longevity:

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[9] In actuality Myriad has "consistently encouraged, promoted and subsidized research on the *BRCA* genes . . . Myriad has provided *BRCA1* and *BRCA2* cDNA clones free to researchers at over 30 research institutions, and conducted collaborative research with more than 440 scientists all over the world . . . [m]ore than 18,000 scientists have . . . published more than 7,000 papers on the genes since Myriad's publication of the genes. (Critchfield Decl., ¶ 65.)

[10] Gaede Decl., Ex. 8.

- The adoption of innovative new drugs is associated with substantial cost savings in medical care. (BARFIELD & CALFEE, BIOTECHNOLOGY AND THE PATENT SYSTEM (2007).)[11]
- Investment and innovation in drugs that offer significant improvements in the treatment, diagnosis or prevention of disease has also had a positive impact on longevity and economic growth. (Frank R. Lichtenberg, *Pharmaceutical Knowledge-Capital Accumulation and Longevity,* in MEASURING CAPITAL IN A NEW ECONOMY (Carol Corrado, John Haltiwanger, and Dan Sichel, eds., 2002).)[12] For example, new drugs arising from pharmaceutical innovation have played a role in the roughly 60% decline in heart disease mortality since the 1960's, and the declining disability rates in the elderly. (BARFIELD & CALFEE, BIOTECHNOLOGY AND THE PATENT SYSTEM (2007).)[13] This same longevity benefit is not found with drugs that are imitative (me-toos) rather than innovative. (Frank R. Lichtenberg, *Pharmaceutical Knowledge-Capital Accumulation and Longevity,* MEASURING CAPITAL IN A NEW ECONOMY (Carol Corrado, John Haltiwanger, and Dan Sichel, eds., 2002).)[14]

The biotechnology industry incurs significant upfront research and development costs for innovative products that can only be recouped by patent protected drugs and diagnostics. Consider:

- Top selling drugs typically have large profit margins because the incremental cost of goods associated with an additional output of production is low. "The industry's high R&D spending and relatively low manufacturing costs create a cost structure similar to that of, for example, the software industry. Both industries have high fixed costs (for research and development) and low variable costs (to put a software application

[11] Gaede Decl., Ex. 9 at p. 5.
[12] Gaede Decl., Ex. 10 at p. 26.
[13] Gaede Decl., Ex. 9 at p. 5.
[14] Gaede Decl., Ex. 10 at p. 26.

onto a CD-ROM or to produce a bottle of prescription medicine). Consequently, prices in those industries are usually much higher than the cost of providing an additional unit of product, because revenue from sales of the product must ultimately cover those fixed costs." (CONGRESSIONAL BUDGET OFFICE, RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY (2006).)[15] This is equally true for diagnostics where there is considerable up front investment.

- "Investors believe that in order for the biotechnology sector to succeed, it is critical that biotechnology firms be able to obtain and enforce strong patents. Biotechnology companies, particularly those that have yet to put a product on the market, must rely on substantial investment funding in order to survive." (CLAUDE BARFIELD & JOHN E. CALFEE, BIOTECHNOLOGY AND THE PATENT SYSTEM (2007).)[16]

A strong patent system correlates with a higher level of research and development. Consider:

- Strong patent protection correlates with the amount of R&D investment, and weak patent laws engender poor investment (without the jobs and economic prosperity which results from this R&D investment). (Henry Grabowski, *Patents, Innovation and Access to New Pharmaceuticals,* 5(4) J. INT'L ECON. LAW 849, 854 (2002).)[17]
- Internationally, the strength of intellectual property protection is positively and significantly associated with R&D. The countries that provided stronger protection tend to have a larger proportions of their GDP devoted to R&D activities. (Sunil Kanwar & Robert E. Evenson, *Does Intellectual Property Protection Spur Technological Change?* (Economic Growth Center Yale University, Discussion Paper No. 831, 2001) *available at* http://www.econ.yale.edu/~egcenter/research.htm.)[18]
- Japan strengthened its patent laws in 1977. Following this change in law, the pharmaceutical industry in Japan "evolved from an imitative entity to an innovative

[15] Gaede Decl., Ex. 11 at p. 4.
[16] Gaede Decl., Ex. 9 at p. 30.
[17] Gaede Decl., Ex. 13 at pp. 853-854.
[18] Gaede Decl., Ex. 12 at p. 22.

one." (Henry Grabowski, *Patents, Innovation and Access to New Pharmaceuticals,* 5(4) J. INT'L ECON. LAW 849, 854 (2002).)[19]

The Congressional Budget Office has cautioned against reducing expectation of profits in the biotechnology industry as that will dampen research and development.

- ". . . changes in price levels also affect firms' expectation about profits. Thus, higher real drug prices may increase the value of completing existing projects more quickly and encourage companies to undertake more new research than they would otherwise. Both effects involve increased R&D spending and thus greater R&D intensity. Analysts generally view that connection as having clear implications for efforts to reduce industry prices and profits, in that such interventions would dampen R&D investment." (CONGRESSIONAL BUDGET OFFICE, RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY (2006).)[20]
- "Economists broadly agree that a reduction in [drug] profits would cause private-sector investment in drug R&D to grow more slowly or to decline." (CONGRESSIONAL BUDGET OFFICE, RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY (2006).)[21]
- Moreover, a recent GAO study found that only 4-6 of the top 100 drugs used by the Department of Defense were developed using government money. Thus, to the extent arguments are raised that government can step in to develop new therapeutics and diagnostics, the objective data is to the contrary: the system relies heavily on private research and development. (UNITED STATES GENERAL ACCOUNTING OFFICE, TECHNOLOGY TRANSFER AGENCIES' RIGHTS TO FEDERALLY SPONSORED BIOMEDICAL INNOVATIONS (GAO-03-536 2003).)[22]

[19] Gaede Decl., Ex. 13.
[20] Gaede Decl., Ex. 11 at p. 10.
[21] *Id*. at p. 45.
[22] Gaede Decl., Ex. 14 at p. 8.

Collectively, the foregoing establishes that the current patent system promotes the introduction of innovative products and services resulting from high research and development spending incurred by private industry that has reduced health care costs and promoted longevity.

IV. ISOLATED DNA SEQUENCES AND METHODS FOR USING THEM ARE PATENTABLE SUBJECT MATTER WITHIN THE CONTEXT OF A PATENT SYSTEM THAT CAREFULLY SCRUTINIZES AND REWARDS PATENTS FOR INVENTIONS CONSISTENT WITH THE CONSTITUTIONAL GRANT

Patents serve the economic purpose of promoting the "progress of science and useful arts by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries." U.S. Const. Art. I, § 8, cl. 8. The time-restricted exclusive right allows the inventor the potential to recover the risk and cost of research, development, regulatory approval and marketing for the patented invention by excluding others from making, using or selling the same invention. In return, the public receives the benefit of a published document – a patent that teaches how to make and use the technology upon expiration of the patent – that would not be available to the public if withheld, *e.g.*, as a trade secret. In most instances the patent application is published prior to grant of the application. If a patent is not granted on a published application either because the inventor abandons the application or the invention is not deemed patent-worthy by the USPTO or later by the U.S. courts, the technology remains in the public domain.

A. SECTION 101 PROVIDES A BROAD SCOPE OF PATENTABLE SUBJECT MATTER THAT REFLECTS THE HAND OF MAN

The United States patent statute codified in Title 35 of the United States Code, is based on a constitutional grant of power to Congress. Section 101's language itself is quite broad, *viz*. "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." The Supreme Court affirmed an expansive view of Section 101 when it upheld genetically engineered bacteria as patentable. *Diamond v. Chakrabarty*, 447 U.S. 303 (1980). That finding was based on broad meanings of the statutory terms "manufacture" and "compositions of matter." *Chakrabarty*, 447 U.S. at 308.

35 U.S.C. § 101 ensures that patents to products derived from natural sources such as DNA or the diagnostic or therapeutic use of DNA are distinguishable from the product of nature itself. In *Chakrabarty* the Supreme Court held that an invention that embraces living matter is not *per se* unpatentable. Limits, however, are imposed on patents that cover products derived from natural sources. "The test set down by the Supreme Court and implemented by the USPTO for patentable subject matter in this area is whether the subject matter sought to be patented is the result of **human intervention**." U .S. Patent & Trademark Office, Manual of Patent Examining Procedure (MPEP) § 2105 (8th ed. 2001) (emphasis added). Thus, patents are not issued to human genes or any other product derived from nature as they exist in the human body. Instead, patents are only issued to inventions after the natural product has been removed from the body by a process of isolation or purification, and identification of structure and utility.

All life science inventions include or coincide with one or more laws of nature. Therefore, if mere inclusion or reliance upon such things would render an invention unpatentable, there could be no medical patents. For this reason, courts have made it clear that, although fundamental principles themselves are not patentable, useful applications of the principles ***are***, so long as the use is specific enough not to "pre-empt" other applications of the principle. *See Mackay Radio & Tel. Co. v. Radio Corp. of Am.*, 306 U.S. 86, 94 (1939); *Diamond v. Diehr*, 450 U.S. 175, 187 (1981). In other words, an invention which is a "nonnaturally occurring manufacture or composition of matter-a product of human ingenuity 'having a distinctive name, character, [and] use'" is patentable. *Chakrabarty*, 447 U.S. at 309-310.

For example, the Federal Circuit recently held that claims utilizing correlations of natural processes in a series of specific steps that are patent-eligible do not pre-empt a fundamental principle, and are therefore patentable. *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 581 F.3d 1336 (Fed. Cir. 2009). Specifically, method of treatment steps involving chemical or physical transformation of physical objects or substances are *per se* patentable, although "every

transformation of physical matter in the body can be described as occurring according to natural processes and natural law."[23] *Prometheus*, 581 F. 3d. at 1346.

In sum, it is the application of human ingenuity, or "the hand of man," that is necessary to achieve patentable subject matter for health care inventions that are inherently intertwined with natural laws. *Chakrabarty*, 447 U.S. at 309. In the case of genetic materials, it is the identification and isolation of a DNA sequence of interest, and association of that sequence to clinically useful disease characteristics, that rise above what exists in nature and renders such inventions patentable. This is consistent with a long line of cases supporting the proposition that natural substances are patentable when they are purified and isolated, and the resulting product has utility. *Kuehmsted v. Farbenfabriken of Elberfield*, 179 F. 701 (7th Cir. 1910) (salicylic acid patentable if isolated into a pure and therapeutically useful product); *Merck & Co. v. Olin Mathieson Chemical Corp.,* 253 F.2d 156 (4th Cir. 1958) (purified vitamin B12 patentable because therapeutically useful). Based on these principles, the USPTO has issued patents for a variety of newly identified gene-based nucleic acid sequences, proteins, and polypeptides that are claimed in a form that differentiates them from naturally occurring substances. Moreover, the MPEP explicitly requires the rejection of any claim whose interpretation as a whole could encompass a human being as an attempt to patent an invention directed to nonstatutory subject matter. MPEP § 2105.

B. COUNTERBALANCED AGAINST A BROAD SCOPE OF PATENTABLE SUBJECT MATTER ARE A NUMBER OF STATUTORY CONDITION PRECEDENTS THAT ENSURE ONLY INVENTIONS PROPERLY DISCLOSED TO THE PUBLIC ARE GRANTED A PATENT

While patentable subject matter has been quite properly viewed expansively consistent with the constitutional grant, Congress enacted a careful statutory scheme to ensure that only truly new and innovative inventions properly conceived of and disclosed to the public are awarded a patent. The conditions precedent to the grant of a patent are set forth primarily in 35 U.S.C. §§ 101-103 and 112. Congress delegated its responsibility to the USPTO to determine

[23] In *Prometheus*, the Federal Circuit also dismissed Justice Breyer's *Metabolite* dissent, upon which Plaintiffs rely to support their Motion for Summary Judgment, as "not controlling law." *Prometheus*, 581 F. 3d. 1346 n3.

which inventions are patent-worthy. The USPTO's MPEP guides patent examiners to the proper interpretation of the patent statute. The claims of the patent rather than the patent's entire disclosure define the exclusory right of the patentee. These claims are the result of a rigorous examination by a trained U.S. patent examiner to ensure that only claims that meet the statutory requirements of 35 U.S.C. §§ 101-103 and 112 are granted. *In re Hiniker Co.*, 150 F.3d 1362, 1369 (Fed. Cir. 1998) ("[T]he name of the game is the claim").

Patents are not granted on inventions that are in use or described in a publication in the public domain. Patented inventions must therefore be novel as required by 35 U.S.C. § 102. For example, a patent to certain antisense DNA sequences was recently denied because a prior art document described similar DNA sequences and how to obtain the sequences the patent applicant sought to patent. *In re Gleave*, 560 F.3d 1331 (Fed. Cir. 2009).

The requirement that a patent only be granted to inventions that are non-obvious is codified in 35 U.S.C. § 103. This statute prevents patents to foreseeable extensions of what was accomplished in the prior art. The analysis allows the combination of disclosures from a multiplicity of prior art references and should consider common knowledge and common sense to assess obviousness in light of the disclosures of the prior art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). Recently, in *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009), the Federal Circuit affirmed the USPTO's denial of a patent on a DNA molecule encoding a protein known as the Natural Killer Activation Inducing Ligand ("NAIL"). The Federal Circuit noted that in this case, the claimed invention was "the product not of innovation but of ordinary skill and common sense." *Kubin*, 561 F.3d at 1359, *citing KSR*, 550 U.S. at 421.

Patent documents must also have sufficient detail to teach one of skill in the art to make and use the invention as claimed and disclose the best mode known to the inventor to make and use the claimed invention. 35 U.S.C. § 112 (enablement and best mode). The purpose of these requirements is to ensure that the patented invention is communicated to the public in a meaningful way so that one can reproduce the technology after patent expiration. *See* MPEP § 2164. 35 U.S.C. § 112 (written description) also requires that the patent document be

sufficiently concise to convey that the inventor had possession of the claimed subject matter as of the filing date of the application. MPEP § 2161. As a practical matter, 35 U.S.C. § 112 (written description) can limit overreaching by inventors trying to claim inventions that might be possible to make from a patent disclosure but had not yet been conceived.

As an example, in *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), *cert. denied*, 528 U.S. 1089 (1998), a claim to a vertebrate cDNA sequence that encodes insulin was held invalid by the Federal Circuit on the ground the patent did not satisfy the written description requirement of the patent code. Moreover, the *en banc* Federal Circuit is currently considering a case involving a biotechnology invention that will likely lead to further refinement of the written description doctrine. *Ariad. Pharm., Inc. v. Eli Lilly & Co.*, 560 F.3d 1366, *vacated by, reh'g., en banc, granted* 332 Fed. Appx. 636 (Fed. Cir. 2009).

Thus, to the extent it is argued, as Plaintiffs have, that the patent grant to Myriad was improper, it is important to remember that the Myriad patents, and the other DNA sequence patents that will be affected by this decision, are the product of, and have survived the gauntlet of, a carefully-conceived statutory, judicial and administrative environment to ensure that only novel inventions are rewarded with a patent. In short, the U.S. Code, as interpreted by the Federal Circuit and implemented by the USTPO, already provides appropriate limitations on patents to the products derived from nature and their uses.

V. TRADITIONAL JUDICIAL REMEDIES PROVIDE APPROPRIATE RELIEF FOR THE ALLEGED HARMS

A. THE PATENT LAW PROVIDES A REMEDIAL FRAMEWORK TO ADDRESS THE ALLEGED HARM

The patent law currently provides for a number of ways to remedy Plaintiffs' perceived harms, if established. There is no need for the type of blunt tools, constitutional or otherwise, that Plaintiffs suggest as these will broadly affect a broad swath of patent landscape and numerous industries involved in the public good.

"It's prudent to refrain from making constitutional rulings that are unnecessary to the resolution of the case. There exists an obligation of the Judicial Branch to avoid deciding

constitutional issues needlessly." *Nat'l Abortion Fed'n v. Ashcroft*, 330 F. Supp. 2d 436, 483 (S.D.N.Y. 2004) (quotations omitted) (*vacated on other grounds*) (citing *Christopher v. Harbury*, 536 U.S. 403, 417 (2002)); *Ashwander v. Tenn. Valley Auth*., 297 U.S. 288, 347 (1932) (Brandeis, J., concurring) and *Burton v. United States*, 196 U.S. 283, 295 (1905)).

Both the Judicial Branch and Congress have been examining patent remedies, giving courts greater flexibility to address harms, while reigning in some of the perceived enforcement excesses that underlie Plaintiffs' arguments. In fact, some of concerns suggested by the Plaintiffs have been effectively addressed by recent judicial efforts to reform patent remedies, and the rest are within the broad and substantial remedial powers granted by the Patent Act and the antitrust laws to protect patentees' interests while preserving the public interest.

1. The Grant of an Injunction is Discretionary with the District Court and Must Not Disserve the Public Interest

Patent remedies, as provided in 35 USC §§ 281 *et seq*., are an integral component of the patentee's social contract. Although research and clinical laboratories, and the patients they serve, may choose to limit their efforts in areas related to Defendants' patents out of apprehension of future injunctions on their innovations or use, the Supreme Court in the landmark 2006 *eBay* decision firmly held that a permanent injunction may only be granted after applying a four part test. *eBay Inc. v. MercExchange, L.L.C*., 547 U.S. 388 (2006) (vacating Federal Circuit damages ruling for infringement of a business method patent).

In *eBay* the Supreme Court unanimously overruled the Federal Circuit's application of its exceptional circumstance rule, used unsparingly to grant injunctive relief to patent holders, in favor of a rule more in line with traditional notions and principles of equity. In rejecting the formerly relatively routine practice of awarding permanent injunctions, barring exceptional circumstance, to prevailing patentees, *eBay* set forth a four-part test that has led to injunctions being denied by the district courts in approximately a quarter of all cases. Most importantly, the application of the four factors is vested within the District Court's sound discretion, but failure to address them is reversible error. *Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1352 (Fed. Cir. 2009).

The new test requires a plaintiff to demonstrate:

(1) That it has suffered an irreparable injury. Courts have looked to past harms to a patentee's market share, revenues, and brand recognition as relevant for determining whether the patentee has suffered an irreparable injury. *I4I L.P. v. Microsoft Corp.*, 2009 U.S. App. LEXIS 28131 (Fed. Cir. Dec. 22, 2009). However, "*lost sales standing alone are insufficient to prove irreparable harm*." *Automated Merch. Sys. v. Crane Co*., 2009 U.S. App. LEXIS 27667 (Fed. Cir. Dec. 16, 2009) (unpublished) (emphasis added). To the extent that the harms result in lost sales, that does not automatically equate to an injunctive right to prohibit future sales.

(2) That remedies available at law are inadequate to compensate for that injury. Courts have found that the difficulty in calculating damages accurately, *Cummins-Allison Corp. v. SBM Co., Ltd.*, 2009 U.S. Dist. LEXIS 106093, at *14 (E.D. Tex. Nov. 13, 2009), or an infringer's inability to pay damages, to be important issues in determining this factor. *Apple Inc. v. Psystar Corp*., 2009 U.S. Dist. LEXIS 116502, at *12-13 (N.D. Cal. Dec. 15, 2009). Although some courts have suggested that the potential for future infringement notwithstanding damages paid for past infringement creates an inadequacy in monetary damages, *Telequip Corp. v. The Change Exchange*, 2006 U.S. Dist. LEXIS 61469, at *4-5 (N.D.N.Y. 2006); *800 Adept, Inc. v. Murex Securities, Ltd*., 505 F. Supp. 2d 1327, 1337-38 (M.D. Fla. 2007) (*rev'd on other grounds),* this would seem to be less of an issue in light of the court's ability to construct an ordered royalty. *Paice LLC v. Toyota Motor Corp*., 504 F.3d 1293 (Fed. Cir. 2007).

(3) The balance of hardships between the plaintiff and defendant favors the plaintiff. The "balance of hardships assesses the relative effect of granting or denying an injunction on the parties, the district court properly considered several factors in its analysis. These factors included the parties' sizes, products, and revenue sources." *I4I*, 2009 U.S. App. at *68.

In fleshing out these factors, district courts applying *eBay* have also generally looked to the parties' competitive relationship, *Hynix Semiconductor Inc. v. Rambus Inc.*, 609 F.Supp.2d 951 (N.D. Cal. 2009); the nature of the relevant market, *Advanced Cardiovascular Sys. v.*

Medtronic Vascular, Inc., 579 F. Supp. 2d 554, 559-560 (D. Del. 2008); and patentee's prior licensing history, *IMX, Inc. v. Lendingtree, LLC*, 469 F. Supp. 2d 203, 225 (D. Del. 2007).

And (4), that the public interest would not be disserved by a permanent injunction. Although equally influential in arguing for or against permanent injunctive relief, this criterion is particularly apropos to the case before this Court. In areas of medical technology, courts scrutinize injunctive relief, particularly when the public's health and safety is potentially at risk. *Advanced Cardiovascular* 579 F. Supp. 2d at 561 (citing precedent showing public harm for injunctions against physician preferred medical devices); *Kimberly-Clark Worldwide, Inc. v. Tyco Healthcare Group LP*, 635 F. Supp. 2d 870, 882 (E.D. Wis. 2009) (noting that an "injunction would mean that some nontrivial number of patients would not be able to receive the treatment their physician preferred").

Thus, while Plaintiffs point to the exclusionary power of Myriad's patents as a perceived abuse warranting judicial intervention at the statutory and constitutional level, that exclusionary power is not automatic, and it need not necessarily result in the alleged harm complained of by Plaintiffs.

2. The Courts Have Been Articulating Higher Standards for Damages and Have Identified the Right of the Defendant to Earn a Profit as an Appropriate Consideration in Granting an Ordered Royalty

In addition to *eBay* and its progeny curbing injunctive remedies, the courts retain other recourses in prospective remedies to make patentees whole while still protecting the public interest. Ordered royalties in particular may be an effective remedy that can be wielded by this Court that does not require a sweeping decision.

In *Paice v. Toyota Motor Corp.*, applying *eBay*'s four factor test, the Federal Circuit found that 35 U.S.C. § 283 provided for an ongoing royalty in lieu of injunctive relief. *Paice*, *supra*, 504 F.3d 1293 (Fed. Cir. 2007). One of *Paice*'s patented drive trains was found to be infringed, under the doctrine of equivalents, by Toyota's hybrid vehicle drive trains. In finding no threat of irreparable harm and the adequacy of monetary compensation, the Federal Circuit affirmed the district court's remedy under the statutory language of 35 USC § 283, including the

ongoing royalty rate of $25 per infringing vehicle for the remaining life of the patent. In his concurrence, Judge Rader reiterated that the court should only impose an ongoing royalty once negotiations between the parties fail.

Judge Folsom in *Paice LLC v. Toyota Motor Corp*., 609 F. Supp. 2d 620, 625 (E.D. Tex. 2009), on remand to reevaluate the ordered royalty rate, noted the change in circumstances by the parties and the market and ruled in favor of a higher ongoing royalty rate, but far less than requested by the plaintiffs. Judge Folsom took pains to distinguish the hypothetical negotiations in determining pre-litigation reasonable royalties for infringed patents, as first described in *Georgia-Pacific Corp. v. United States Plywood Corp.,* 318 F. Supp. 1116 (S.D.N.Y. 1970) (*see also Rite-Hite Corp. v. Kelley Co.,* 56 F.3d 1538 (Fed. Cir. 1995) (*en banc*)), from post litigation on-going royalty rate determinations applicable only once a judgment of validity and infringement has been entered. Nonetheless, Judge Folsom found that the ordered royalty analysis permitted consideration of the adjudicated defendant's profits, and did not warrant an automatic trebling of damages even though as an adjudicated infringer, the defendant would be a willful patent infringer. As this decision shows, the Court has considerable flexibility to fashion an appropriate remedy under ordered royalty principles, if appropriate, that do not require the sweeping relief Plaintiffs request here.

In addition to the *Paice* decision approving of ordered royalties, courts have further been examining more closely arguments of damage by patentees. Patent damages are designed to be compensatory, not retributive. *Pall Corp. v. Micron Separations*, 66 F.3d 1211, 1223 (Fed. Cir. 1995). Lost profits, typically the greater of the available awards, cannot be granted unless the two parties are in direct competition. *BIC Leisure Prods. v. Windsurfing Int'l*, 1 F.3d 1214, 1218 (Fed. Cir. 1993). Plaintiffs argue that Myriad's patents prevent patients seeking a second opinion through a test provided by another entity, or deprive services to indigent patients who

cannot pay for Myriad's allegedly high-priced test.[24] Of course, if true, a second opinion from a second provider, by definition, cannot be competition as it is a medical second opinion, nor is providing a test to indigent women competitive to Myriad, as such women cannot pay for Myriad's test and there are no lost sales to Myriad.

And while in the past plaintiffs have attempted to bolster damage awards determined by the alternative reasonable royalty analysis, the courts and the legislature are focusing on ensuring that such awards are reasonable. *See, e.g.* Mark A. Lemley, *Distinguishing Lost Profits from Reasonable Royalties*, William & Mary Law Review 51:655 (2009).[25] To this end, the Federal Circuit has attempted to better concretize the methods for determining the pre-litigation royalty rates. *See, e.g.*, *Lucent Techs. v. Gateway, Inc.*, 580 F.3d 1301 (Fed. Cir. 2009); *American Seating Co. v. USSC Group, Inc.,* 514 F.3d 1262 (Fed. Cir. 2008) (Entire Market Value Rule inapplicable when infringing product was sold with non-infringing product for convenience only).

Judge Rader of the Federal Circuit, sitting by designation in the Northern District of New York, recently penned a decision that discusses how a court should properly focus its damages analysis and rejected the plaintiffs' overreaching theories. *Cornell Univ. v. Hewlett-Packard Co*., 609 F. Supp. 2d 279 (N.D.N.Y. 2009) (severely curtailing the rewarded royalties to the patentees based on the actual contribution of the infringing component to the demand for the product from which the royalty base is derived).

The Federal Circuit in 2007 also heightened the standards necessary to obtain a finding of willful patent infringement with its attendant potential trebling of damages. *In re Seagate Tech., LLC*, 497 F.3d 1360 (Fed. Cir. 2007) (*en banc*). The Federal Circuit's decision, overruling a twenty-year standard, has substantially limited the patentee's ability to threaten treble damages for willful infringement, a claim that had become de rigueur in nearly every infringement claim.

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[24] Notwithstanding the reality that it often does not make good economic or medical sense for patients to obtain second opinion testing, nothing prevents patients from seeking second opinions with genetic counselors and physicians on their test results. Further, there are multiple licensed laboratories and research studies that can perform second opinion testing. (Critchfield Decl. ¶¶ 61-63.)

[25] Gaede Decl., Ex. 15.

See, e.g., Judge Kimberly Moore, *Empirical Statistics on Willful Patent Infringement*, 14 Fed. Cir. B.J. 227 (2004).[26]

These judicial decisions all show that Plaintiffs' alleged perceived harms of overreaching potential damage awards dampening competition is empty rhetoric that does not require this Court to wade into broad statutory and constitutional issues that may impact the advancement of healthcare in this country.

3. The Antitrust Laws Also Limit Overreaching Enforcement of Patent Rights

A recent publication by the Federal Trade Commission and the Department of Justice reconcile antitrust and intellectual property law as "complementary bodies of law that work together to bring innovation to consumers." U.S. Dep't of Justice & Fed. Trade Comm'n, *Antitrust Enforcement and Intellectual Property Rights: Promoting Innovation and Competition* (2007).[27] Anti-competitive enforcement of intellectual property rights can run afoul of antitrust law, particularly when those actions extend beyond the statutory patent grant. *CSU, L.L.C. v. Xerox Corp. (In re Independent Serv. Orgs. Antitrust Litig.)*, 203 F.3d 1322 (Fed. Cir. 2000). To the extent that a patentee attempts to extend control over their patents beyond their statutory term or scope, this Court has recourse to apply antitrust laws to prevent such abuse that does not require a determination that may effectively strike down an entire class of patents.

VI. PATENTS ON DNA SEQUENCES AND GENE-BASED DIAGNOSTIC METHODS DO NOT IMPLICATE THE FIRST AMENDMENT

A. PATENT LAW ENCOURAGES THE PUBLIC DISSEMINATION OF INFORMATION IN EXCHANGE FOR EXCLUSIVITY TO ACTIONS (NOT SPEECH OR THOUGHTS) CONSTITUTING THE PERFORMANCE OF THE INVENTION

1. Disclosure in Patents Promotes the Exchange of Ideas

In exchange for a grant of exclusivity over the use of an invention, a patentee must disclose the best mode and sufficient details to enable one skilled in the art to perform the invention. This is the antithesis of "government limiting knowledge." (Plaintiffs' Motion, p. 33.)

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[26] Gaede Decl., Ex. 16.
[27] Gaede Decl., Ex. 17 at p. 3.

2. Companies Will Resort to Trade Secret, Inhibiting the Flow of Information

Without patents, many companies will turn to trade secret protection for data from clinical trials, now open to physicians and patients to inform decision-making, and thus will no longer be available to the public for evaluation of the strength of technology/statistical analysis. This will inhibit scientific discussion, analysis, and criticism of new diagnostics and technology, and may impede potential improvements normally gained by design-around attempts driven by potential for exclusivity on an improved invention.

B. IT IS ACTIONS OF INFRINGEMENT THAT ARE PROTECTED, NOT THOUGHT OR SPEECH

Plaintiffs divide the claims in the seven patents at issue into two categories: (1) claims for reaching conclusions about DNA sequences, and (2) claims over DNA sequences themselves. Plaintiffs argue that each of these categories is unconstitutional because they conflict with the First Amendment. These arguments are ill-founded and should be rejected.

1. The Experimental Use Defense Harmonizes Patent Law With the First Amendment

Plaintiffs argue that the First Amendment limits the scope of intellectual property laws and that the copyright laws expressly recognize this limitation by providing the fair use defense to infringement. (Plaintiffs' Motion, pp. 32-33.) Plaintiffs, however, do not discuss the "experimental use" defense in patent law, thus suggesting that patent law is insensitive to the First Amendment.

For almost 200 years, the patent laws have recognized an affirmative defense to patent infringement that is analogous to the fair use defense in copyright law. In *Whittemore v. Cutter,* 29 Fed. Cas. 1120, 1121 (C.C.D. Mass. 1813), Justice Story recognized that infringing actions carried out for research purposes did not give rise to liability. The Federal Circuit continues to recognize this defense, *see, e.g.*, *Madey v. Duke Univ.,* 307 F.3d 1351, 1360-63 (Fed. Cir. 2002); *Embrex, Inc. v. Serv. Eng'g Corp.*, 213 F.3d 1343, 1349 (Fed. Cir. 2000); and Congress has extended it by statute in some instances. *See* 35 U.S.C. § 271(e)(1).

2. Patent Law Encourages the Public Dissemination of Information in Exchange for Exclusivity to Actions (Not Speech or Thoughts) Constituting the Performance of the Invention

As the Supreme Court has repeatedly recognized, the patent system is based upon a *quid pro quo*—in exchange for the limited rights granted by a patent, inventors disclose to the public the details of their inventions. *See, e.g., Eldred v. Ashcroft*, 537 U.S. 186, 214-16 (2002); *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred International, Inc.,* 534 U.S. 124, 142 (2001) ("The disclosure required by the Patent Act is 'the *quid pro quo* of the right to exclude.'" (*quoting Kewanee Oil Co. v. Bicron Corp.,* 416 U.S. 470, 484 (1974)). Without strong patent protection, companies will resort to trade secret protection and the store of public knowledge will be depleted.

Recognizing that patents provide an important incentive for research and public disclosure, recent studies of the patent system have not recommended expanding the experimental use defense or declaring patents on isolated DNA sequences and their uses to be unpatentable. *See, e.g.*, Fed. Trade Comm'n, *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy* (2003), available at http://-www.ftc.gov/os/2003/-10/innovationrpt.pdf.[28]

3. Infringing Acts, not Thought or Speech, Violate a Patentee's Right To Exclude

To support their constitutional arguments, Plaintiffs mischaracterize the claims of the patents at issue. In particular, Plaintiffs assert that five of the patent claims involve "looking at" one or more DNA sequences and reaching some conclusion about them, and that a sixth claim involves a mental process of comparing cell growth rates. Plaintiffs argue that these claims unconstitutionally grant a monopoly over certain thoughts. (Plaintiffs' Motion, pp. 34-35.)

Plaintiffs' argument ignores the totality of these claims' language and wrongly focuses on a single, possibly mental, step – that which Plaintiffs assert is the only unique part of the invention. In so doing, Plaintiffs are committing a legal error. The Federal Circuit and the Supreme Court have stated that there is no legally recognizable or protected essential element,

[28] Gaede Decl., Ex. 18.

gist or heart of the invention in a patent claim. *In re Bilski*, 545 F.3d 943, 994 (Fed. Cir. 2008) (*en banc*), *cert. granted Bilski v. Doll*, 129 S. Ct. 2735 (2009); *W.L. Gore & Assocs. v. Garlock, Inc.,* 721 F.2d 1540, 1548 (Fed. Cir. 1983). Each of these claims requires specific physical actions to determine the useful DNA sequence before any analysis or comparison can be performed. Just as claimed inventions cannot be dissected to determine patent eligibility under 35 U.S.C. § 101, *Diehr,* 450 U.S. at 188, claims should not be dissected to determine whether they implicate constitutional concerns.

Similarly, Plaintiffs argue that claims to the isolated DNA sequences are unconstitutional because they give "entire control over a body of knowledge and over pure information to a private company." (Plaintiffs' Motion, p. 37.) This is simply inaccurate – the claims are limited to isolated nucleic acids, which are specific compositions of matter. The information conveyed by these nucleic acids can be used in many ways without infringing the patents. *First*, experiments which do not require creation of any nucleic acids encoding all or a portion of a gene sequence, *e.g.* computer modeling, likely can be performed. *Second*, molecular biologists have techniques available that can be used to perform studies of genes without creating them in isolated form. *Third*, some experiments, particularly non-commercial experiments, that use the claimed isolated nucleic acids, may qualify as noninfringing experimental uses. *Fourth*, many owners of patents claiming isolated DNA sequences will grant low-cost or free research licenses to facilitate research.

VII. THE MYRIAD PATENT CLAIMS ARE VALID UNDER ARTICLE 1, SECTION 8, CLAUSE 8

A. THE MYRIAD PATENTS AT THEIR CORE REFLECT THE TANGIBLE WORK BY MAN TO IDENTIFY THE CHEMICAL STRUCTURE OF A SPECIFIC DNA SEQUENCE AND THUS IS A USEFUL DISCOVERY SQUARELY WITHIN THE SCOPE OF THE PATENT CLAUSE

At the core, Plaintiffs misapprehend what is fundamentally reflected in Myriad's patent claims: a tangible chemical structure that is stated by the means of DNA sequence terminology. This tangible DNA sequence is certainly a new and useful "discovery" that was not known before. (Indeed, Plaintiffs' act of filing suit reflects the fundamental utility of the

discovery.) Further, as claimed, the Myriad patent claims reflect a chemical structure not found in man.

Thus, to the extent Plaintiffs argue that the claims impinge on thought or expression, or somehow impede progress, they are wrong. The verbal expression of the particular chemical structures claimed is no different than the verbal expression of any other patented chemical structure. While one can make the argument that in the short term, a specific patent impedes progress through the constitutional authorized grant of a limited monopoly, the Patent Clause itself reflects that the Founders understood that overall, such limited monopolies would advance science.

B. CONGRESS IS THE PROPER ENTITY TO DETERMINE WHETHER DNA SEQUENCE CLAIMS AND METHODS FOR USING THEM ARE PATENTABLE

The question of whether so-called gene patents impede progress or promote progress is a uniquely public determination to be made by Congress, where the pros and cons of such patents can be weighed. In fact, Congress has considered the issue in the past, and has left the current patent system in place.

For example, in 2002 Representative Lynn Rivers (D-MI) introduced into Congress the Genomic Research and Diagnostic Accessibility Act ("GRDAA"),[29] a bill that would have provided limited exemptions from liability for certain uses of patented genetic sequences and genetic sequence information in the context of basic research and genetic diagnostic testing. Importantly, the GRDAA would not have affected the patentability of genetic inventions. The bill received little support.

In 2007, Rep. Xavier Becerra (D-CA) introduced the Genomic Research and Accessibility Act (GRAA),[30] which would prospectively bar the patenting of any "nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies." This legislation received little support and was not passed.

[29] H.R. 3967, 107TH CONGRESS, 2D SESSION (Mar. 14, 2002) (Gaede Decl., Ex. 19).
[30] H.R. 977, 110TH CONGRESS, 1ST SESSION (Feb. 9, 2007) (Gaede Decl., Ex. 20).

As long ago as 1993, the Senate did not pass the Life Patenting Moratorium Act, which would have placed a two-year moratorium on DNA sequence patents in order to provide time for Congress to assess issues related to these types of patents.[31]

Collectively, this legislative history reflects (1) Congress' understanding that DNA sequence patents are properly within the Scope of Section 101 and hence the Patent Clause, and (2) an implicit determination that DNA sequence patents under the current patent system in fact do promote the "progress of Science," within the meaning of the Patent Clause. *Amici* respectfully request that the Court take notice of this legislative record and defer to Congress the societal issue of whether DNA sequence patents promote or impede the "Progress of Science."

VIII. CONCLUSION

For the foregoing reasons *Amici Curiae* respectfully request that Plaintiffs' motion for summary judgment be denied.

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Respectfully submitted,

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[31] S. 387, 103D CONGRESS, 1ST SESSION (Feb. 18, 1993) (Gaede Decl., Ex. 21).